



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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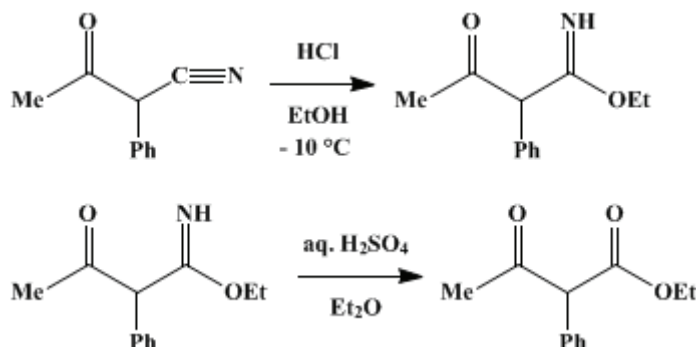
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 2, p.284 (1943); Vol. 18, p.36 (1938).

ETHYL α -PHENYLACETOACETATE

[α -Toluic acid, α -acetyl-, ethyl ester]



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1. Procedure

The apparatus consists of a 1-l. three-necked flask with a mercury-sealed mechanical stirrer and a 6-mm. inlet tube reaching to the bottom of the flask. In the third neck is a cork bearing a low-temperature thermometer and a tube containing phosphorus pentoxide on glass wool, and calcium chloride. The inlet tube is connected to three 20-cm. drying towers, two containing phosphorus pentoxide on glass wool, and one containing calcium chloride. To the last tower is connected a 2-l. Florence flask fitted as a wash bottle with a safety tube and containing 1 l. of concentrated sulfuric acid. The Florence flask is connected to the hydrogen chloride generator described in *Org. Syn. Coll. Vol. I, 1941, 293*, in which a single charge of 1.5 l. of concentrated sulfuric acid and 800 cc. of hydrochloric acid is sufficient for this preparation. A pressure equalizer should be provided between the generating flask and the funnel.

After the inlet tube is removed from the reaction flask, 400 cc. of absolute alcohol (Note 1) and 161 g. (1 mole) of dry α -phenylacetonitrile (m.p. 88.5–89.5°) (p. 487) are added. The neck is temporarily closed by a cork, and the nitrile is dissolved by warming with stirring. The flask is then surrounded by a freezing mixture, and the solution vigorously stirred, so that any nitrile which crystallizes will be finely divided. When the temperature reaches -10° , the inlet tube is inserted and a stream of dry hydrogen chloride passed through, with moderate stirring, at such a rate that the bubbles rising from the 6-mm. tubing in the sulfuric acid wash bottle can just be counted. This is continued for five to eight hours until the mixture is saturated (Note 2). The ice bath is then removed, stirring continued until all the solid has dissolved (about one hour), and the flask allowed to stand overnight (Note 3).

Most of the excess hydrogen chloride is removed by adding porous tile and evacuating the flask with a water pump for a half hour, while it is surrounded by a water bath maintained at about 40° . Two hundred grams of sodium carbonate is dissolved in 1.2 l. of water in a 5-l. flask, and 2 l. of cracked ice added. Into this solution the reaction mixture is poured in a thin stream with vigorous shaking, and the solution is extracted at once with three 500-cc. portions of ether. The ether extracts are washed countercurrently with four 250-cc. portions of ice-cold 5 per cent sodium chloride solution to remove the alcohol and then combined in a 3-l. flask placed in an ice bath.

A solution of 100 g. of c.p. concentrated sulfuric acid in 700 cc. of water is prepared in a 5-l. flask, 1.5 l. of cracked ice added, and the mixture shaken until ice forms on the outside of the flask. After about half of this solution has been poured into the cold ether solution of the imino ether, using a funnel to remove the excess ice, the mixture is shaken for exactly fifteen seconds (Note 4), allowed to settle, and the layers separated. The remaining acid is added to the ether layer in two portions, the mixture each time being shaken for fifteen seconds, and separated. Since the ether solution, although now free of

the imino ether, still contains a small amount of [ethyl phenylacetoacetate](#), it is saved to be combined with the main portion later.

The [sulfuric acid](#) solution of the imino ether sulfate quickly turns cloudy because of the separation of [ethyl \$\alpha\$ -phenylacetoacetate](#). To complete the hydrolysis, the mixture is heated on the steam bath for one-half hour at the temperature at which the [ether](#) just boils (about 50°) ([Note 5](#)). It is then cooled, the ester layer separated, and the acid extracted once with 250 cc. of [ether](#). The [ether](#) solution is washed once with 100 cc. of water which is recombined with the acid. The acid solution is replaced on the steam bath and heated for forty-five minutes after the temperature reaches 80–90°. After the solution is cooled and extracted as before, all [ether](#) extracts, including the original from which the imino ether was removed, are combined and washed once with 250 cc. of 5 per cent [sodium bicarbonate](#) solution, once with 250 cc. of water, and then dried over 20 g. of anhydrous [sodium sulfate](#) ([Note 6](#)). The [sodium sulfate](#) is removed by filtration and washed with [ether](#), the [ether](#) removed from the filtrates, and the residue fractionated *in vacuo* from a 250-cc. Claisen flask having a 25-cm. fractionating side arm. The main fraction boils at 139–143°/12 mm., or 130–134°/5 mm., and weighs 103–167 g. (50–81 per cent of the theoretical amount). By fractional distillation of the fore-run, main fraction, and residue, a product boiling over a one- to two-degree range may be obtained with no change in the yield ([Note 7](#)).

2. Notes

1. The alcohol was dried once with lime, and once with [sodium](#), according to [Note 1, Org. Syn. Coll. Vol. I, 1941, 251](#).
2. More rapid saturation lowers the yield appreciably.
3. A fine precipitate, probably [ammonium chloride](#), settles. The most successful runs showed little or none of this precipitate.
4. Any delay at this point results in hydrolysis of some of the imino ether to the product, which stays in the [ether](#) layer.
5. Care should be taken in lifting the flask from the bath, since any mixing may cause the [ether](#) to boil out of the flask.
6. Removal of product from time to time during the course of the hydrolysis seems to improve the yield.
7. The liquid ester is an equilibrium mixture, the enol content of which is increased by distillation and falls slowly, on standing, to 30 per cent.¹ The boiling point of 145–147°/11 mm., recorded in the literature, is higher than any noted in the present work.

3. Discussion

[Ethyl \$\alpha\$ -phenylacetoacetate](#) can be prepared by the hydrolysis of [\$\alpha\$ -phenylacetonitrile](#) in absolute [alcohol](#) with dry [hydrogen chloride](#).¹ The present method differs in specifying neutralization of the [hydrogen chloride](#) with [sodium carbonate](#) and hydrolysis of the imino ether in aqueous [sulfuric acid](#), so that the product separates as fast as it forms. This protects the ester from further decomposition, and a considerably increased yield results.

References and Notes

1. Beckh, Ber. **31**, 3160 (1898); Post and Michalek, J. Am. Chem. Soc. **52**, 4358 (1930).
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

α -Toluic acid, α -acetyl-, ethyl ester

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride,
hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

Ethyl α -phenylacetoacetate (5413-05-8)

α -phenylacetonitrile (4468-48-8)

ethyl phenylacetoacetate